

REMARKS

Applicants have received and reviewed the Office Action dated May 20, 2009. By way of response, Applicants present the following remarks and the accompanying Declaration.

Applicants respectfully submit that pending claims 23-27 are in condition for allowance, and notification to that effect is earnestly solicited.

Rejection of Claims Under 35 U.S.C. § 103(a)

The Examiner rejected claims 23-27 under 35 U.S.C. § 103(a) as obvious over Fisher et al., WO02/42290, in view of Fountoulakis et al., *J. Chromatography A*, 1998, and the Sigma-Aldrich catalog. Applicants respectfully traverse this rejection.

The Present Invention

Applicants tested several organic acids and discovered that only one of them, methanesulfonic acid, was a suitable reagent for hydrolyzing loratadine to desloratadine. This invention is reflected in presently pending claim 1. This desloratadine unexpectedly lacks an impurity found in other preparations of desloratadine.

Applicants respectfully submit that it was unpredictable that an organic acid, much less one specific organic acid, would be effective in this reaction. Applicants submit herewith a Declaration Under 37 C.F.R. § 1.132 describing the results of testing five organic acids for their ability to convert loratadine to desloratadine. Three of these organic acids – trifluoroacetic acid, trichloroacetic acid, and formic acid – did not hydrolyze loratadine to desloratadine. One of the five - p-toluene sulfonic acid –hydrolyzed loratadine to desloratadine slowly and in poor yield. Only one of the five - methanesulfonic acid – effectively converted loratadine to desloratadine. It was unpredictable that an organic acid would convert loratadine to desloratadine. Further, it was unpredictable that methanesulfonic acid would be the only organic acid to prove effective in this reaction.

On the basis of this unpredictability, Applicants respectfully submit that the presently claimed invention is patentable in light of a primary reference disclosing mineral acids for this reaction and secondary references relating to hydrolysis of the amide bonds of peptides and proteins. Applicants respectfully request withdrawal of this rejection.

The Primary Reference Discloses a Reaction Using Mineral Acids, Not an Organic Acid

WO 02/42290 discloses a process of converting loratadine to desloratadine by reacting the loratadine with a concentrated mineral acid, such as sulfuric acid, hydrochloric acid, or hydrobromic acid (WO 02/42290 at pages 4-7). The reaction is hydrolysis that removes the urethane moiety (a carbamate moiety) from loratadine to yield “double salts” of desloratadine.

In a separate anion exchange reaction - not a hydrolysis reaction - these double salts of desloratadine can be converted to simple salts by exposure to strong base and another acid. The table at page 8 of WO 02/42290 reports the results of converting the double salts to salts of several organic acids, including the methanesulfonate salt and the p-toluenesulfonate salt. Again, this is merely the exchange of the anion of the salt and not a hydrolysis reaction.

The WO 02/42290 reference fails to disclose or suggest employing an organic acid, such as methanesulfonic acid, in converting loratadine to desloratadine. And, the Examiner acknowledged this fact in the Office Action. As described above, it was unpredictable that any organic acid, much less the claimed methanesulfonic acid, would be effective in converting loratadine to desloratadine.

The Court of Appeals for the Federal Circuit recognizes that chemistry is often an unpredictable art. *Esai Co. Ltd v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Thus, the prior art is less likely to identify predictable solutions. *Id.* In such an unpredictable art, obviousness requires a prediction in the prior art of the results obtainable from a selected component. *Abbott Laboratories v. Sandoz, Inc.*, 533 F.3d 1341, 1351 (Fed. Cir. 2008). In this case, the selected component is the organic acid, methanesulfonic acid. The WO 02/42290 reference fails to provide any prediction that an organic acid, such as methanesulfonic acid, might be suitable for converting loratadine to desloratadine. This reference discloses only to mineral acids in this reaction. These shortcomings of this primary reference are not remedied by the secondary references.

Further, the cited references must establish a reasonable expectation of success in achieving the claimed invention. The Federal Circuit court in *Pfizer v. Apotex*, 480 F.3d, 1348, 1366, 82 U.S.P.Q.2d 1321, 1334 (Fed. Cir. 2007) noted that reasonable expectation of success is not established where the prior art teaches merely to pursue a general approach that seemed promising in the field of experimentation or gave only general guidance as to particular form of the claimed invention or how to achieve it. At best, the primary reference might be said to

suggest trying acid hydrolysis of loratadine to desloratadine. However, this reference provides no expectation that any organic acid, much less methanesulfonic acid, would work in this reaction. The demonstrated lack of predictability of the function of organic acids as reported in the accompanying Declaration provides factual evidence of this lack of expectation of success. Again, the secondary references do not remedy these shortcomings of this primary reference.

The Secondary References Do Not Remedy the Shortcomings of the Primary Reference

The Office Action attempts to remedy the shortcomings of WO 02/42290 using two secondary references relating to hydrolytic degradation of peptides and or proteins to their constituent amino acids. This reaction is hydrolysis of the amide bonds in peptides or proteins to yield the amino acids that make up the peptide or protein. Applicants respectfully submit that hydrolysis of peptide bonds is not predictive of or relevant to the claimed hydrolysis of a carbamate.

In addition, one of the secondary references, the Fountoulakis reference, concludes that methanesulfonic acid is not a preferred acid for hydrolysis reactions, stating, “[i]n spite of obvious advantage, routine use of methanesulfonic acid in protein hydrolysis is less popular than that of HCl” (emphasis added, page 112, last line, and page 113). Thus, the cited Fountoulakis reference would steer the skilled artisan away from the claimed method, which uses this less popular acid.

In addition, the Fountoulakis reference discloses that *p*-toluenesulfonic acid can be used for hydrolysis of the amide bonds of proteins. In contrast, this acid was not useful for converting loratadine to desloratadine; the reaction was very slow and yield was too low (see above and the accompanying Declaration). It appears that hydrolysis of carbamates is unpredictable compared to the use of acids in hydrolysis of amide bonds of peptides. The accompanying Declaration also provides additional information establishing that cleavage of carbamates is unpredictable. Thus, the hydrolysis of carbamates is unpredictable in light of disclosure of the same acids used in hydrolysis of amide bonds of peptides and proteins.

There are additional differences between carbamate hydrolysis and protein hydrolysis as well. In protein hydrolysis the task is to liberate all amino acids of the peptide or protein and to quantitatively recover them. Thus, these secondary references also address whether or not certain amino acids can be identified after hydrolysis of all of the peptide bonds by the acid. For

example, the Fountoulakis reference discloses that hydrolysis employing methanesulfonic acid can result in improved recovery of tryptophan and methionine sulfoxide residues (see, e.g. pages 112 and 113). Recovery and identification of amino acids is not relevant to the claimed hydrolysis of a carbamate.

The combination with the secondary references fails to establish any greater degree of predictability than the primary reference. Absent a teaching of predictability, the claimed invention is not obvious. *Esai v. Dr. Reddy's, supra*; *Abbott Laboratories v. Sandoz, Inc., supra*. The combined references fail to provide any prediction that an organic acid, such as methanesulfonic acid, might be suitable for converting loratadine to desloratadine. The disclosure of the secondary references with respect to amide bonds of peptides is not relevant to cleaving the carbamate moiety from loratadine to yield desloratadine.

The combination with the secondary references fails to establish any more reasonable expectation of success than the primary reference. Absent such a reasonable expectation, the claimed invention is not obvious. *Pfizer v. Apotex, supra*. The combined references fail to provide any expectation that a skilled worker would be successful in employing an organic acid, such as methanesulfonic acid, for converting loratadine to desloratadine. Again, the disclosure of the secondary references with respect to amide bonds of peptides is not relevant to cleaving the carbamate moiety from loratadine to yield desloratadine.

Conclusion

Accordingly based on the foregoing differences, Applicants respectfully submit that the cited references neither teach nor suggest the presently claimed process and withdrawal of this rejection is earnestly solicited.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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